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The Use of Jet-Injectors in BCG Vaccination*

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In mass vaccination programmes, the jet-injection of vaccine may have considerable operational advantages over the classical techniques. The technical performance of two models of jet-injector, the Dermo-Jet and the Ped-O-Jet, in BCG vaccination was assessed in a number of studies which are reviewed by the authors. It is shown that the jet-injectors do not administer the full dose for which they are calibrated and that the size of the vaccination lesion varies more than after vaccination by syringe.

By increasing the dosage considerably, the results of vaccination by jet-injection may be improved to a certain extent but the risk of unpleasant reactions is also increased.

Jet-injectors have been used for many years as an alternative to the needle and syringe for administering subcutaneous injections and, more recently, for the percutaneous application of vaccine in smallpox vaccination. The main advantages of jet-injectors are that, to an extent varying with the model, they are easy to handle and readily accepted by children and, in particular, their use allows, under certain circumstances, a large number of vaccinations to be made in a short time. With these advantages, the instruments are obviously highly attractive for use in mass vaccination programmes.

Jet-injectors may be equipped with a nozzle that causes the vaccine to be deposited intradermally. Such a nozzle is used in smallpox vaccination and the results, in general, compare favourably with those obtained by the classical percutaneous techniques. It seemed possible that the same instruments might also be used to administer BCG vaccine although the careful intradermal injection of an exact dose is essential for this vaccination procedure. Investigations were prompted by operational considerations; many smallpox and BCG vaccination programmes can profitably be combined into a single programme. However, when smallpox vaccination is given by jet-injector, it is generally held that BCG vaccine must be given in the same way, so that the combined programme is not retarded by a slower BCG vaccination technique.

MATERIAL AND METHOD

There is no simple way of estimating the immunity in man conferred by BCG vaccination; to assess the quality of the vaccination, use has to be made of various circumstantial effects. The most important of these is perhaps tuberculin sensitivity, which is invariably induced by vaccination, even if the BCG vaccine is of poor quality. This allergic response may not be directly related to immunity, but it is a quantitative phenomenon that varies with the dose of vaccine effectively given; the latter can thus be measured by means of a low-dose post-vaccination test—at least in persons who had no tuberculin sensitivity before vaccination (Edwards, Palmer & Magnus, 1953; WHO Tuberculosis Research Office, 1955a; Guld, 1957). It is important to realize that the level of tuberculin sensitivity after superficial and deep intradermal inoculations, and also after subcutaneous injections, is the same (Palmer & Edwards, 1953). Therefore, the studies reviewed in this paper have been based on the premise that any

* This article is a review of a number of investigations sponsored by, or made in co-operation with, the World Health Organization. The studies were carried out in France (C. Fillastre, G. Conge & E. Orssaud), in Gabon (C. Gateff), in Korea (A. Tanaka), in Nicaragua (O. Ortega Ramirez & H. G. ten Dam), in Niger (R. Collas & J. Wright) and in Senegal (L. Chambon, M. Barme, U. B. Tommasi, H. Sarrat, P. Bres, L. Diallo & M. Gauthier). The basic protocol for the studies and this review were prepared by H. G. ten Dam, Scientist, in consultation with M. Piot and J. Guld, Medical Officers, Tuberculosis, World Health Organization, Geneva. Separate reports of the studies in mimeographed form and reprints of this article are available to persons officially or professionally interested on request to Tuberculosis, World Health Organization, 1211 Geneva, Switzerland.

difference between the vaccination techniques would be merely quantitative, at least as regards the post-vaccination tuberculin sensitivity.

The allergic response to vaccination differs from individual to individual, even when a constant dose is administered in a uniform population. However, when vaccination and tuberculin testing have been performed properly, and when the vaccine used has not been too weak, the tuberculin reactions will show a normal, or at least a unimodal, statistical distribution. Thus, in general, the distribution is adequately characterized by the mean and the variance. A disadvantage in the use of the allergic response for such assessment, and especially in comparisons, is that the level of tuberculin sensitivity, as revealed by a low-dose post-vaccination test, varies only slightly with the dose of vaccine administered. As an indication, for the usual strengths of vaccine and tuberculin, a dose of vaccine 10 times larger than the standard dose will result in a tuberculin reaction that is on average about 3 mm larger in diameter than that produced by the standard dose. Thus a large study population may be required to reveal the, presumably, small differences in allergic response resulting from similar vaccination techniques. Other effects that may be considered for assessing the quality of a vaccination are the local wheal that immediately follows an inoculation, the induration appearing in a few days at the inoculation site and the local lesion and scar which develop later. These effects depend, at least quantitatively, on the dose of vaccine but probably also on the injection technique and they are therefore unsuitable for comparing different vaccination techniques.

A further effect, which apparently does not depend on the technique of injection and which is strongly related to the dose administered, is the occurrence of lymphadenitis, generally several months after vaccination. With strong vaccines, this unpleasant reaction is fairly common in new-born infants (Guld et al., 1955) but for obvious ethical reasons a study cannot be designed to make use of this effect. With the usual vaccine doses, and especially in schoolchildren (who represent a far more convenient study population), the phenomenon is rare.

Although local indurations, lesions and scars, as well as the incidence of lymphadenitis, are unsuitable as indications for assessing the positive qualities of the vaccination techniques, they are effects that may limit the application of BCG vaccine and, as such, they must be carefully considered.

In view of the current interest in direct BCG vaccination and re-vaccination, the populations included in most studies belonged to several epidemiological classes which, ideally, should be considered separately—namely, children who, according to the initial tuberculin test, are non-reactors and have not been vaccinated before (no BCG scar present), children who are reactors but who have not been vaccinated before, and children who have been vaccinated before (BCG scar present). It should be noted that the latter group cannot be divided into non-reactors and reactors by means of the usual tuberculin test because the level of tuberculin sensitivity in vaccinated persons does not depend only on vaccination but also on tuberculin testing (Guld et al., 1968).

The allergenic effect of vaccination is best measured in non-reactors who have not previously been vaccinated, but in most studies this group was not singled out. Thus in Nicaragua, where more than half of the children had been vaccinated before, the results were analysed separately for those who had been vaccinated previously and for those who had not. Differences in post-vaccination tuberculin reactions between the various vaccination groups could therefore be expected to be relatively small since, after vaccination, the tuberculin sensitivity in reactors changes very little. Nevertheless, since the differences observed appeared to be statistically significant, no further subdivision into reactors and non-reactors was made.

In the other studies, non-reactors and reactors were considered separately, but in several instances previously vaccinated children were not excluded from these groups. The inclusion of these children, who may have shown increased tuberculin sensitivity as a result of repeated tuberculin testing, could possibly have masked differences between the vaccinated groups, especially if the vaccination technique was less effective.

The side-reactions, in particular the vaccination lesions, are generally more violent in reactors and in previously vaccinated children, and these groups are therefore of particular interest in this respect. In the studies reviewed here, the effects of vaccination were measured in terms of the post-vaccination tuberculin reactions 9–15 weeks after vaccination, the induration at the site of injection 3–4 days after vaccination, and the local lesion (tissue destruction) 9–15 weeks after vaccination. On the occasion of the latter examination, the presence of axillary and cervical lymph node enlargement was also investi-

TABLE 1

POST-VACCINATION TUBERCULIN REACTIONS, LOCAL INDURATIONS AND VACCINATION LESIONS IN SCHOOLCHILDREN VACCINATED WITH BCG [a] BY SYRINGE OR BY DERMO-JET; KOREA STUDY

Population group and concentration of vaccine [b] (dose = 0.1 ml)	Means of administration	Tuberculin reaction after 15 weeks			Local induration after 3 days			Vaccination lesion after 15 weeks		
		No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Non-reactors without BCG scar										
Standard vaccine	Syringe	285	6.2	38.4	320	3.3	4.4	295	5.3	5.8
	Dermo-Jet	252	4.5	36.0	282	2.2	5.3	258	3.0	7.8
Concentrated vaccine	Syringe	274	8.9	38.4	297	3.8	5.3	281	6.7	7.3
	Dermo-Jet	266	6.7	42.3	298	3.1	9.6	271	4.2	10.2
Reactors without BCG scar										
Standard vaccine	Syringe	93	18.0	23.0	98	7.5	9.0	94	7.6	5.3
	Dermo-Jet	75	18.1	13.0	86	5.4	16.8	76	5.3	11.6
Concentrated vaccine	Syringe	83	18.6	16.0	89	7.9	10.9	83	9.3	7.8
	Dermo-Jet	103	19.0	6.3	113	9.1	31.4	103	6.3	7.8
Children with BCG scar										
Standard vaccine	Syringe	45	13.2	42.3	52	5.0	7.3	47	6.0	5.3
	Dermo-Jet	53	10.3	53.3	58	3.8	7.3	58	5.0	13.0
Concentrated vaccine	Syringe	39	11.6	39.7	46	5.9	9.6	40	8.0	4.8
	Dermo-Jet	56	12.6	39.7	58	5.4	15.2	57	6.9	16.0

[a] Vaccine; Glaxo batch F10.

[b] The concentrated vaccine was 2½ times more concentrated than the standard vaccine.

gated, although this was probably not the most suitable time for determining absolute frequencies.

Except in Gabon, where the study was carried out among the general population, all the investigations were carried out in schoolchildren. During the first visit, the children were given a low-dose tuberculin test (1 TU or 2 TU of batch RT 23 with Tween 80 or 10 units of IP 48) and in several studies the children were examined for existing BCG scars. At the same time they were either vaccinated or given a placebo according to a random allocation. Post-vaccination testing was done with similar doses of tuberculin and all reactions (indurations, lesions, tuberculin reactions) were measured in millimetres. Enlarged lymph nodes were generally recorded in 1-cm groups. Further details on the composition of the groups in the different studies may be found in Tables 1–6.

Two types of jet-injector were tested—namely, the manually operated Dermo-Jet [1] and the foot-operated Ped-O-Jet.[2] For purposes of comparison, in all studies at least one group of children was vaccinated, according to the routine procedure, by syringe (Omega microstat) and needle (Eisele, platinum).

In several studies, two or more different concentrations or volumes of vaccine were used with a view to determining which dose administered by jet-injector would correspond most closely to the classical vaccination. In these instances, the instruments were generally used in rotation in the various eligible groups vaccinated by jet-injector in order to avoid differences arising from variations between one instrument and another.

Only a few jet-injectors could be used in each study and these few instruments may not have been entirely representative of the particular model. In addition, the operators had had relatively little experience with jet-injectors which, if experience

[1] Manufactured by Société AKRA, Pau, France.

[2] Manufactured by the Scientific Equipment Manufacturing Corporation, Lodi, N.J., USA.

TABLE 2

POST-VACCINATION TUBERCULIN REACTIONS; LOCAL INDURATIONS AND VACCINATION LESIONS IN SCHOOLCHILDREN VACCINATED WITH BCG [a] BY SYRINGE OR BY DERMO-JET; NICARAGUA STUDY

Population group and concentration of vaccine [b] (dose = 0.1 ml)	Means of administration	Tuberculin reaction after 10 weeks			Local induration after 3 days			Vaccination lesion after 10 weeks		
		No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Children without BCG scar										
Standard vaccine	Syringe	185	10.8	37.6	210	5.7	12.3	195	5.8	4.8
	Dermo-Jet	225	9.8	41.6	240	5.8	21.8	231	4.7	6.5
Concentrated vaccine	Syringe	180	11.7	30.3	208	7.1	22.0	196	7.1	6.0
	Dermo-Jet	199	10.0	42.6	221	6.4	21.8	206	5.4	5.7
Children with BCG scar										
Standard vaccine	Syringe	307	12.0	26.4	333	7.1	9.3	322	6.4	2.9
	Dermo-Jet	310	11.2	28.9	334	7.4	19.3	322	6.1	5.7
Concentrated vaccine	Syringe	325	13.0	19.2	359	8.6	17.3	337	7.8	5.5
	Dermo-Jet	298	11.5	24.8	329	8.4	24.8	309	6.6	3.4

[a] Vaccine; Glaxo batch F10.
[b] The concentrated vaccine was 2½ more concentrated than the standard vaccine.

counts, may have influenced unfavourably the results obtained with these instruments.

RESULTS

In some studies, the various vaccination groups, which had been formed by random allocation, showed slight differences, e.g., in the level of pre-existing tuberculin sensitivity, but in all cases these differences are satisfactorily explained as probable consequences of the allocation procedure and they will hardly have influenced the comparisons.

In all studies, except those in France, there was at least one unvaccinated control group; thus it could be shown directly that the vaccine used had an allergenic effect. In the studies in Korea, Nicaragua, Senegal and Gabon a placebo (diluent) was administered by jet-injector and it could therefore be shown that the weakest vaccine dose administered

TABLE 3

POST-VACCINATION TUBERCULIN REACTIONS, LOCAL INDURATIONS AND VACCINATION LESIONS IN SCHOOLCHILDREN VACCINATED WITH BCG [a] BY SYRINGE OR BY PED-O-JET; NIGER STUDY

Population group and vaccine	Means of administration	Tuberculin reaction after 13 weeks			Local induration after 3–4 days			Vaccination lesion after 13 weeks		
		No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Non-reactors	Syringe	148	13.4	13.2						
0.1 ml of 0.3 mg/ml vaccine	Ped-O-Jet	198	11.1	18.5						
Reactors and non-reactors	Syringe				232	13.7	17.2	232	6.5	11.6
0.1 ml of 0.3 mg/ml vaccine	Ped-O-Jet				296	9.9	16.0	296	5.0	12.9

[a] Vaccine employed: Glaxo batch T17D.

TABLE 4

POST-VACCINATION TUBERCULIN REACTIONS AND VACCINATION LESIONS IN SCHOOLCHILDREN VACCINATED WITH BCG BY SYRINGE OR BY PED-O-JET; SENEGAL STUDIES

Population group and vaccine	Means of administration	Tuberculin reaction after 3 months			Vaccination lesion after 3 months		
		No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Non-reactors 0.1 ml of 0.5 mg/ml vaccine [a]	Syringe Ped-O-Jet	43 43	9.4 10.1	17.6 24.6	43 43	4.8 3.5	3.1 6.6
Reactors 0.1 ml of 0.5 mg/ml vaccine [a]	Syringe Ped-O-Jet	44 48	13.4 12.6	22.6 28.2	45 48	5.0 4.6	4.5 8.9
Non-reactors 0.1 ml of 0.35 mg/ml [b] vaccine [c]	Syringe	121	14.8	15.5	123	3.4	1.3
Non-reactors 0.15 ml of 0.35 mg/ml [b] vaccine [c]	Ped-O-Jet	123	14.2	21.0	123	3.3	2.6
Reactors 0.1 ml of 0.35 mg/ml [b] vaccine [c]	Syringe	171	17.7	17.2	172	3.7	1.3
Reactors 0.1 ml of 0.35 mg/ml [b] vaccine [c]	Ped-O-Jet	167	18.0	17.2	168	4.2	3.7

[a] Vaccine employed: IPD batch E43.
[b] Half of each group was given the vaccine in half this strength. [c] Vaccine employed: IPD batch 66-59 B.

in this way still produced measurable tuberculin sensitivity and that the lesions that developed were in fact due to BCG and were not, for example, merely effects due to the injection of a liquid.

The mean values and variances for the post-vaccination tuberculin reactions, local indurations and vaccination lesions observed in the various groups are summarized in Tables 1–6.

As regards the post-vaccination tuberculin reactions, the most interesting populations are those of non-reactors and of children not previously vaccinated; the distributions for most of these are shown in Fig. 1–6. A comparison of the groups given equal (or supposedly equal) doses of the same vaccine shows that those vaccinated by jet-injector had a lower mean tuberculin reaction than those vaccinated by syringe. In most instances the differences were shown to be statistically significant but there is one exception. In the preliminary study in Senegal the group vaccinated by Ped-O-Jet actually showed a higher mean than the group vaccinated by syringe, but the 5% confidence limits of the difference of the means are -1.3 and $+2.8$, and this finding therefore does not contradict the general pattern.

These results were furthermore confirmed in a Dermo-Jet study in Poland (Dr T. Olakowski, personal communication). In this study, follow-up examinations were carried out 6 and 12 months after vaccination. In children who were non-reactors only one strength of vaccine was used (0.5 mg/ml). The mean diameters of the post-vaccination reactions to 2 TU of batch RT 23 plus Tween 80 and of the scars, together with the variances, are given in Table 7.

In all studies, total absence of a tuberculin reaction was observed more frequently in the groups vaccinated by jet-injector, as may be seen from Fig. 1–6. The variances were nevertheless mostly similar but as the means in the jet-injector groups were consistently smaller it is probable that the dose was not always administered as effectively by jet-injector as it was by syringe. Anticipating such a result, most workers included different vaccine dos-

TABLE 5

POST-VACCINATION TUBERCULIN REACTIONS AND VACCINATION LESIONS IN A GENERAL POPULATION VACCINATED WITH BCG [a] BY SYRINGE OR BY PED-O-JET; GABON STUDY

Population group and vaccine	Means of administration	Tuberculin reaction after 9 weeks			Vaccination lesion after 9 weeks		
		No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Non-reactors							
0.10 ml of 1 mg/ml vaccine	Syringe	58	12.4	14.8	58	4.8	1.8
	Ped-O-Jet	60	11.5	17.6	60	4.4	5.7
0.15 ml of 1 mg/ml vaccine	Ped-O-Jet	46	12.2	15.8	46	5.8	11.5
0.15 ml of 0.5 mg/ml vaccine	Ped-O-Jet	82	11.5	12.2	82	5.2	7.7
0.10 ml of 1.5 mg/ml vaccine	Ped-O-Jet	64	9.0	24.9	65	3.6	7.0
Reactors							
0.10 ml of 1 mg/ml vaccine	Syringe	75	14.9		75	5.9	2.7
	Ped-O-Jet	74	14.2		74	5.1	7.1
0.15 ml of 1 mg/ml vaccine	Ped-O-Jet	70	14.2		70	6.4	10.8
0.15 ml of 0.5 mg/ml vaccine	Ped-O-Jet	83	14.3		83	5.8	9.3
0.10 ml of 1.5 mg/ml vaccine	Ped-O-Jet	83	14.3		83	5.0	6.1

[a] Vaccine employed: IPD batch 6832.

TABLE 6

POST-VACCINATION TUBERCULIN REACTIONS AND VACCINATION LESIONS IN SCHOOLCHILDREN VACCINATED WITH BCG [a] BY SYRINGE OR BY PED-O-JET; FRANCE STUDY

Population group and vaccine	Means of administration	Tuberculin reaction after 9 weeks			Vaccination lesion after 9 weeks		
		No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Non-reactors	Syringe	181	15.6	8.5	182	7.7	2.1
0.10 ml of 0.5 mg/ml vaccine	Ped-O-Jet	180	13.3	14.6	181	6.2	3.3
Non-reactors	Syringe	183	15.5	8.0	184	8.5	3.0
0.10 ml of 1 mg/ml vaccine	Ped-O-Jet	182	13.8	16.3	183	7.0	5.3

[a] Vaccine employed: IPP batch 155.

ages in their studies, in order to determine whether, by increasing the dose, the " loss " of vaccine could be compensated. That such a compensation is possible is shown in the results obtained in Korea (Table 1 and Fig. 1). A vaccine 2½ times as concentrated as the standard vaccine [1] gave, when administered by a Dermo-Jet instrument, a slightly higher mean tuberculin reaction than vaccine of standard

[1] Instead of the 5 ml prescribed by the manufacturer, 2 ml only of reconstitution fluid was used.

TABLE 7

POST-VACCINATION TUBERCULIN REACTIONS AND VACCINATION SCARS, 6 AND 12 MONTHS AFTER BCG VACCINATION OF SCHOOLCHILDREN IN POLAND [a]

Population	Time after vaccination	Means of administration	Tuberculin reaction			Vaccination scar		
			No. of subjects	Mean size (mm)	Variance	No. of subjects	Mean size (mm)	Variance
Non-reactors without an old BCG scar	6 months	Syringe	50	11.2	19.4	50	4.2	2.4
		Dermo-Jet	40	10.2	28.4	40	2.8	2.2
	12 months	Syringe	26	11.5	22.4	65 [b]	4.8	2.8
		Dermo-Jet	40	8.6	23.9	77 [b]	2.9	3.2
Non-reactors with an old BCG scar	6 months	Syringe	80	14.3	16.3	80	5.3	1.6
		Dermo-Jet	89	11.9	23.6	89	4.2	2.5
	12 months	Syringe	60	13.8	22.8	127 [b]	5.9	2.0
		Dermo-Jet	66	12.5	24.3	151 [b]	4.8	2.7

[a] Polish vaccine, batch 357106; individual dose: 0.05 mg/0.1 ml.
[b] Including the children also examined 6 months after vaccination.

concentration delivered by syringe while the variances were similar. The lower 5% confidence limit of the difference of the means is –0.4 mm. This effect was however not seen in Nicaragua where the same vaccines and the same model of Dermo-Jet were used; a satisfactory explanation for the discrepancy cannot be given.

In the studies with the Ped-O-Jet instrument, dosages were included that had been increased by 50% or 100%. These increases were obviously not large enough. From Tables 3–6 and Fig. 2–6 it may be seen that the higher doses administered by Ped-O-Jet in no instance gave the same (or a higher) mean tuberculin reaction as the lower doses delivered by syringe. In a few instances the values may seem quite close, for example, a dose of 0.15 ml administered by Ped-O-Jet (compared with 0.10 ml given by syringe) gave promising results in both Senegal and Gabon. Nevertheless, in these instances the lower 5% confidence limits of the differences in the mean between the Ped-O-Jet and syringe groups are −1.5 mm and −1.8 mm, respectively; this may represent a considerable difference in dose. To conclude that a still higher dose given by jet-injector would have resulted in the same reaction as a standard dose (0.10 ml) given by syringe would, therefore, be speculative.

Although the mean tuberculin reactions associated with the higher doses administered by jet-injector were not altogether satisfactory, the variances were similar to those observed after vaccination by syringe. Thus the variation in doses administered by jet-injector may not be greater than that in doses injected by syringe. Therefore it appears that the jet-injectors systematically injected a certain proportion of the dose.

The size of the local induration 3–4 days after vaccination appeared to vary independently of the technique of vaccination. A single observation of an evolving reaction provides little basis for comparison and no conclusions with respect to the effectiveness of the jet-injection technique can be drawn. The observation does, however, show that vaccination by jet-injection gave rise to no serious effects at this time.

To a certain extent, the comments on single observations apply also to lesion size, but 10 weeks or more after vaccination most lesions have passed the evolutive stage and comparisons are generally considered to be justified. From Tables 1–6 and

FIG. 1

TUBERCULIN REACTIONS AND VACCINATION LESIONS 15 WEEKS AFTER BCG VACCINATION BY SYRINGE OR BY DERMO-JET IN NON-REACTORS WITHOUT AN OLD BCG SCAR; KOREA STUDY

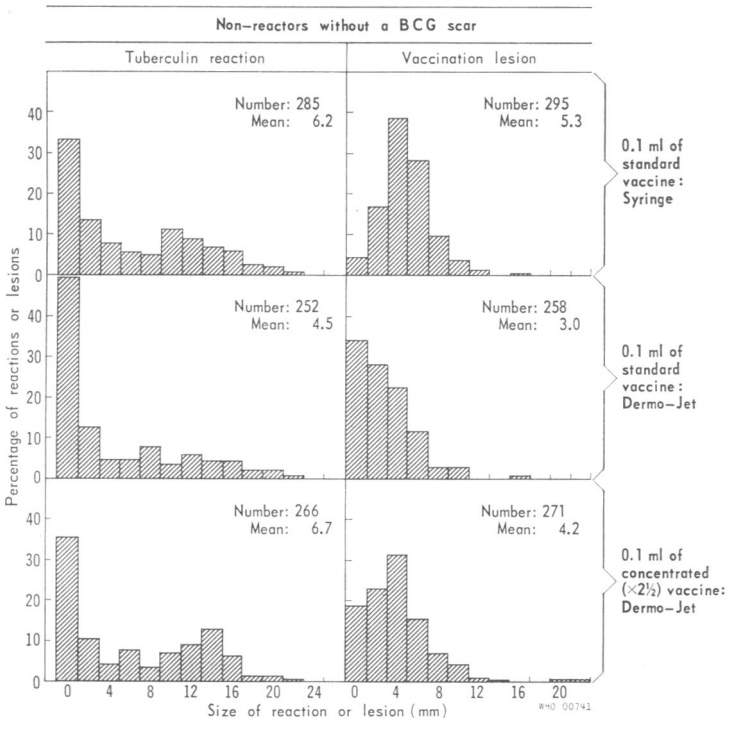
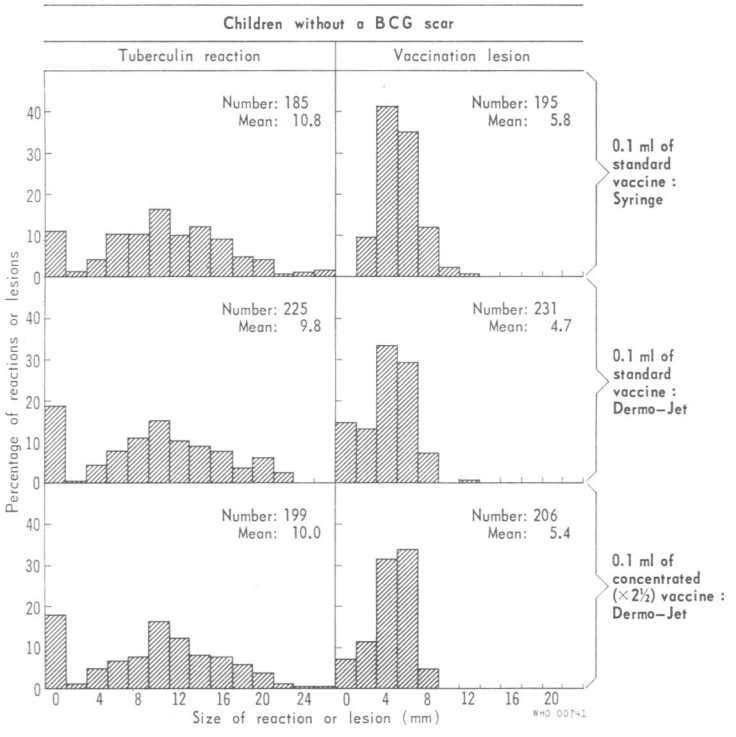


Fig. 1–6 it can be seen that, for equal vaccine doses, the lesions produced by jet-injection are invariably smaller than those resulting from injection by syringe. The means of injection may have influenced the lesion size, but the findings are also compatible with a smaller dose having been effectively injected, as the observations on post-vaccination tuberculin reactions indicated. Total absence of a lesion was more frequent in the groups vaccinated by jet-injector, as may be seen from Fig. 1–6, and in some instances it was correlated with total absence of tuberculin sensitivity, indicating that jet-injection sometimes failed entirely. It is important to notice in Tables 1–6 that the variation of vaccination lesions in the groups vaccinated by jet-injector is generally greater than that in comparable groups vaccinated by syringe. As the variation of the tuberculin reactions between the groups is similar, it seems possible that there are individual differences in the way the vaccine particles are deposited.

As might have been expected, higher doses of vaccine, whether given by syringe or by jet-injector, produced larger lesions than smaller doses. Nevertheless, in Korea (Table 1, Fig. 1) the stronger dose administered by Dermo-Jet gave rise to a mean lesion that was smaller than that produced by the weaker dilution administered by syringe, in both non-reactors and reactors, the differences being statistically significant at the 5% level. However, in previously vaccinated children in Korea, the mean lesion in those vaccinated by Dermo-Jet seemed to be larger.

Since the mean tuberculin reaction was larger in non-reactors given the stronger vaccine by Dermo-Jet than in those given the weaker dose by syringe, the result of the vaccination by Dermo-Jet can, on the whole, be considered favourable, even though variations in size of the lesions in the Dermo-Jet groups were larger and some lesions more than 20 mm in diameter were seen.

FIG. 2
TUBERCULIN REACTIONS AND VACCINATION LESIONS 10 WEEKS AFTER BCG VACCINATION BY SYRINGE OR BY DERMO-JET IN CHILDREN WITHOUT AN OLD BCG SCAR; NICARAGUA STUDY



In the study in Nicaragua and the studies with the Ped-O-Jet instrument the results were less favourable. In several instances, and notably when the more satisfactory tuberculin reactions were observed, both the mean size and the variation in size of lesions resulting from vaccination by jet-injector were greater than those associated with vaccination by syringe; in no instance, however, was the same, or a higher, mean tuberculin reaction observed.

The frequency of enlargement of axillary lymph nodes on the vaccination side differed from country to country, as may be seen from Table 8 in which the results for all vaccinated children have been combined for each country. A high frequency of enlarged lymph nodes attributable to vaccination was seen only in Niger. In the group vaccinated by Ped-O-Jet the frequency of enlargement was significantly higher ($P < 0.05$) than in the group vaccinated by syringe. Unfortunately, no placebo was administered by Ped-O-Jet in this study; thus, no further conclusions can be drawn. The relatively large numbers of enlarged lymph nodes observed in the Nicaragua study cannot be attributed to BCG vaccination, since the frequency was as high in the controls as in the vaccinated groups. Moreover, of the 53 enlarged nodes observed, 26 were found in the group of 247 children who received a placebo by syringe and the other 27 were in the group of 240 children who were given a placebo by Dermo-Jet infection. In all studies, the lymph nodes observed were rather small, their adherence to the skin (which may indicate suppuration at a later stage) was rare and suppuration did not occur. It should be kept in mind, however, that this complication may have been more frequent at a later stage.

ADDITIONAL OBSERVATIONS

Some studies were not limited to the original protocol; thus, in Senegal, follow-up examinations were

TABLE 8

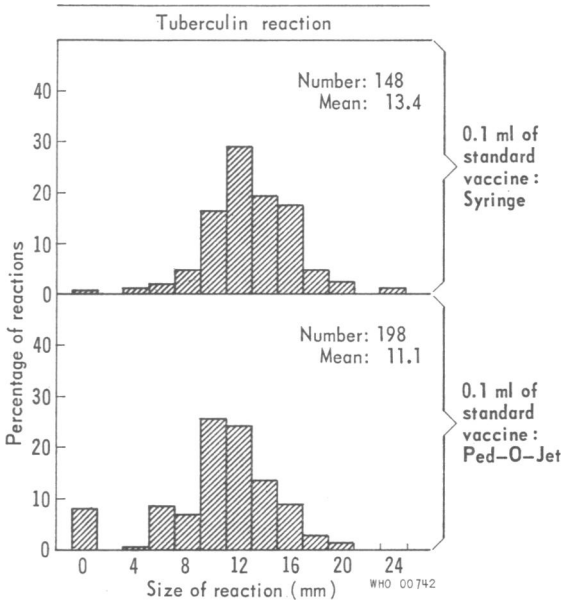
FREQUENCY OF ENLARGEMENT OF AXILLARY LYMPH NODES ON THE SAME SIDE OF THE BODY AS THE VACCINATION IN STUDIES IN FIVE COUNTRIES

Country	Controls		Syringe		Jet-injector	
	No. of subjects	No. of enlarged lymph nodes	No. of subjects	No. of enlarged lymph nodes	No. of subjects	No. of enlarged lymph nodes
Korea	372	0	835	5	820	3
Nicaragua	487	53	997	107	1 032	97
Niger	157	9	232	35	296	67
Senegal	123	5	226	14	231	8
France			365	6	362	4

more frequent. Observations 9 months after vaccination confirm the results that have already been mentioned. The relative performances of the 3 Ped-O-Jet instruments employed were studied by comparing the wheals produced by the injection. The variances of the mean wheal size appeared to differ significantly and the authors have emphasized that the instruments should be maintained in good mechanical condition. The local wheal was also measured in studies made in France; as in Senegal, it was observed that the variance in the Ped-O-Jet group was much larger than in the syringe group. Moreover, some laboratory tests were carried out in the French studies. Vaccine, when delivered by the Ped-O-Jet instrument, showed a larger variation in the number of culturable particles than when seeded by pipette on the culture medium. Colorimetric determination of the volume delivered per dose showed similar dose-to-dose variations.

FIG. 3

TUBERCULIN REACTIONS 13 WEEKS AFTER BCG VACCINATION BY SYRINGE OR BY PED-O-JET IN NON-REACTORS; NIGER STUDY



DISCUSSION

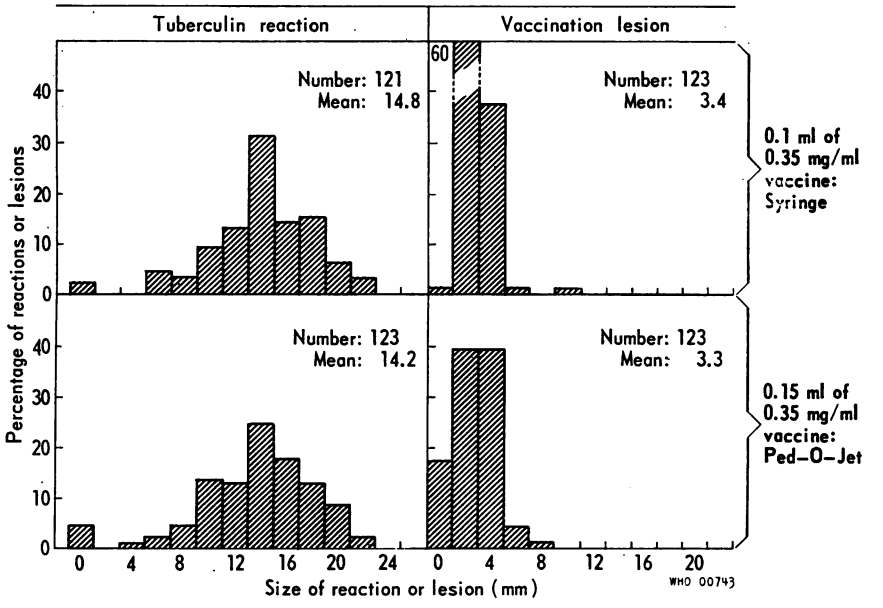
As a general conclusion it may be said that the jet-injectors appeared not to inject the entire dose for which they were calibrated. The importance of this characteristic and ways in which the results might be improved are discussed below.

These considerations are closely connected with the problem of BCG vaccine dosages and are therefore, in part, theoretical since it is, in fact, not known what dose of BCG vaccine will provide the maximum protection in man and it has therefore been the custom to administer the largest possible dose, i.e., a dose that produces not more than a tolerable number of local, and especially regional, complications such as suppurative lymphadenitis. It has been shown in controlled field trials that such a dose produces protection in man, and it is also known to produce post-vaccination tuberculin sensitivity almost as high as that attributable to infection with virulent mycobacteria.

If the dose is reduced, the post-vaccination sensitivity is less and it must also be presumed that the

FIG. 4

TUBERCULIN REACTIONS AND VACCINATION LESIONS 3 MONTHS AFTER BCG VACCINATION BY SYRINGE OR BY PED-O-JET IN NON-REACTORS; SENEGAL STUDY



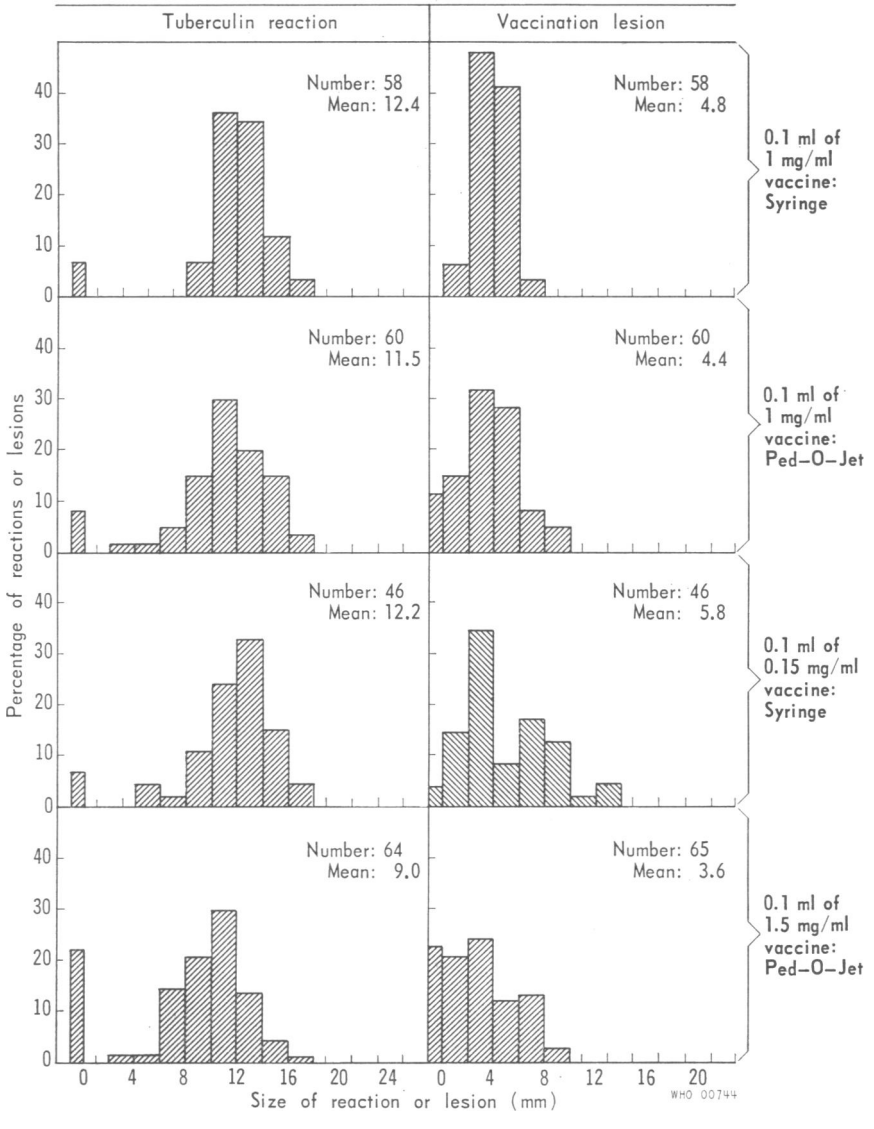
protection will be less, since until now there has been no evidence from prospective studies in man that this is not the case. Any reduction in dosage, other than that needed to reduce the number of complications to a tolerable level, is therefore unjustifiable. Consequently, even the slightest reduction in post-vaccination allergy, which may indicate a considerable reduction in dosage, should be avoided. When using a jet-injector it therefore seems advisable to increase the dosage in order to obtain a level of post-vaccination tuberculin sensitivity that is at least as great as that which occurs after vaccination by syringe. Unfortunately, this procedure will affect the size of the lesion. The results so far obtained indicate that the mean lesion size will probably not be excessively large, but that the variation may be considerably greater than after vaccination by syringe. Therefore, when the dose is increased, the number of excessively large lesions must be expected to be relatively high. In practice, it is the frequency of large lesions, rather than the mean lesion size, that determines the acceptability of vaccination. This greater variation in lesion size therefore limits the possibility of increasing the dose given by jet-injector. However, in most countries, the present practice is to allow a, perhaps unjustifiably, large safety margin; thus an adequate increase should often be possible.

As regards the means of increasing the vaccine dose, either the concentration of vaccine or the volume delivered may be increased, as indicated in Tables 1–6. The former method was more or less successful in Korea but seemed to fail in the studies in Nicaragua and in France. In Niger, only one dose was given by jet-injector; in Senegal, the vaccine was administered in standard and 50% strengths but, as significant differences were not obtained, the separate results have not been reported. In Gabon, both methods of increasing the dosage were used; increasing the volume seemed to produce a better result but it should be remarked that a single instrument was used in each group. The differences observed may therefore have been the result of technical differences between instruments.

In new-born infants, suppurative lymphadenitis, rather than the local lesion, is the most serious side-reaction. Its incidence has been shown to vary strongly with the dose (Guld et al., 1955; WHO Tuberculosis Research Office, 1955b). In none of the studies discussed in this article was special attention given to new-born infants and a general recommendation to use an increased dose of BCG when

FIG. 5

TUBERCULIN REACTIONS AND VACCINATION LESIONS 9 WEEKS AFTER BCG VACCINATION BY SYRINGE OR BY PED-O-JET IN NON-REACTORS; GABON STUDY



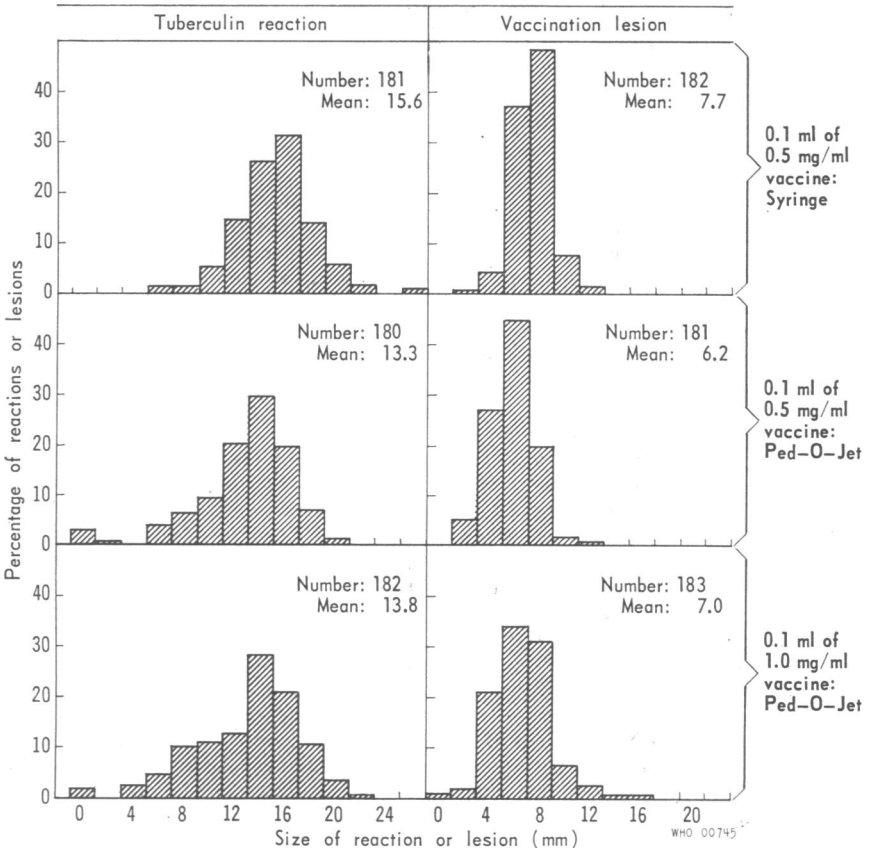
vaccinating by means of jet-injector does not apply to this group. More studies are, therefore, required.

The present studies were not designed to assess the operational aspects of BCG vaccination by jet-injector but some incidental observations are worth mentioning. The vaccination procedure seemed to be relatively easy. Handling of the instruments, however, required a greater physical capacity than vaccination by syringe and the maintenance and repair of the instruments appeared to require some skill or even special facilities. In this connexion, it was remarked that the vaccinator who does not check the local wheal may not notice a sudden failure of the instrument.

The vaccination output can be considerably higher than in a programme of conventional vaccination

FIG. 6

TUERCULIN REACTIONS AND VACCINATION LESIONS 9 WEEKS AFTER BCG VACCINATION BY SYRINGE OR BY PED-O-JET IN NON-REACTORS; FRANCE STUDY



by syringe provided that large numbers of subjects are waiting in line for vaccination and that there are no formalities (such as registration) to be applied. In practice, such a situation may be rare.

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RÉSUMÉ

EMPLOI D'INJECTEURS SOUS PRESSION POUR LA VACCINATION AU BCG

Les résultats à attendre, sur le plan technique, de l'emploi pour la vaccination au BCG de deux types d'injecteurs sous pression, le Dermo-Jet et le Ped-O-Jet, ont été évalués au cours d'une série d'études menées sous les auspices ou avec la participation de l'OMS au Sénégal, au Niger, en Corée, au Nicaragua, au Gabon et en France.

Dans chacune de ces études, on a comparé les rendements respectifs de l'injection sous pression et de la vaccination classsique pratiquée au moyen d'une seringue et d'une aiguille. Les résultats ont été estimés en termes de sensibilité tuberculinique postvaccinale, des dimensions de l'induration et de la destruction tissulaire locales et de l'incidence des hypertrophies ganglionnaires régionales.

La vaccination pratiquée à l'aide d'un injecteur calibré de manière à fournir la même dose (0,1 ml) que la seringue suscite une sensibilité tuberculinique de valeur moindre que celle que confère la vaccination par la technique classique. On peut obtenir de meilleurs résultats en augmentant la dose de vaccin injectée sous pression. Ainsi, en Corée, l'injection par Dermo-Jet d'une dose 2,5 fois supérieure a entraîné un niveau de sensibilité tuberculinique comparable à celui obtenu par injection à la seringue d'une dose simple. Par contre, lors d'essais pratiqués dans les mêmes conditions au Nicaragua, aucun effet analogue n'a été observé. Dans les études menées avec le Ped-O-Jet, les doses n'ont pas été augmentées de plus de 50 à 100%. Bien qu'apparemment plus élevé qu'après administration d'une dose simple, le niveau de la sensibilité tuberculinique ainsi réalisé n'a en aucun cas atteint celui résultant de l'injection à la seringue d'une dose simple.

Si les dimensions moyennes des réactions tuberculiniques, après vaccination sous pression, étaient plus petites, les variances, en revanche, étaient du même ordre qu'après vaccination à la seringue. Il semble donc qu'avec les injecteurs, et de façon systématique, seule une certaine proportion de la dose soit effectivement introduite dans la peau. D'autre part, pour des doses égales de vaccin, l'injection sous pression provoquait des lésions vaccinales dont les dimensions moyennes étaient plus petites qu'après la vaccination à la seringue. Cette observation est compatible avec la conclusion, énoncée ci-dessus, selon laquelle la dose réellement injectée est plus faible, mais il se peut aussi qu'elle soit le résultat direct de l'emploi d'une technique d'injection différente. La variance des lésions provoquées par la vaccination sous pression était plus élevée que celle des lésions succédant à la vaccination classique. La variance des réactions tuberculiniques étant similaire avec les deux techniques, il est possible qu'il existe des différences individuelles dans les modalités d'introduction du vaccin dans la peau.

Dans toutes les études autres que celle menée en Corée, les dimensions moyennes des lésions, et en particulier leurs variances, ont été plus élevées après administration d'une dose plus forte par injection sous pression qu'après injection à la seringue d'une dose simple. La différence était particulièrement nette pour les dosages qui conféraient un niveau plus satisfaisant de sensibilité tuberculinique postvaccinale. L'importance pratique de cette observation ne peut être négligée, car cela limite les possibilités d'augmenter les doses administrées par injection sous pression.

Au Niger, on a relevé une plus forte incidence des hypertrophies ganglionnaires après emploi du Ped-O-Jet qu'après vaccination à la seringue. Ailleurs, la fréquence de ce genre de réaction a été du même ordre dans les deux groupes de sujets vaccinés.

Selon les auteurs, il convient, si l'on utilise l'injecteur sous pression, d'augmenter les doses individuelles de façon à obtenir un niveau de sensibilité tuberculinique postvaccinale équivalant à celui qui résulte de la vaccination par la technique classique, mais alors le risque de réactions indésirables s'accroît également.

REFERENCES

Edward, L. B., Palmer, C. E. & Magnus, K. (1953) *BCG vaccination*, Geneva, (*World Health Organization: Monograph Series*, No. 12), pp. 51-64

Guld, J. (1957) *Bull. Wld Hlth Org.*, **17**, 225-248

Guld, J. et al. (1955) *Brit. med. J.*, **2**, 1048-1054

Guld, J. et al. (1968) *Bull. Wld Hlth Org.*, **39**, 829-836

Palmer, C. E. & Edwards, P. Q. (1953) *Brit. med. J.*, **1**, 363-368

WHO Tuberculosis Research Office (1955a) *Bull. Wld Hlth Org.*, **12**, 123-141

WHO Tuberculosis Research Office (1955b) *Bull. Wld Hlth Org.*, **12**, 143-167